FORM PTO-1390 (REV. 9-2001) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY 'S DOCKET NUMBER: 740-X01-004

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 10/018372

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/05208	7 June 2000	12 June 1999

TITLE OF INVENTION
PLASTICALLY DEFORMABLE IMPLANT

APPLICANT(S) FOR DO/EO/US
Dirk-Henning MENZ and Joachim DRESP

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [x] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [x] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [x] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [x] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [x] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [x] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [x] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [x] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [x] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [x] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [x] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [x] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [x] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [x] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [x] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [x] Other items or information:
    FORMAL DRAWINGS (1 SHEET)
    MARKED-UP SPECIFICATION
    COPIES OF REFERENCES CITED IN IDS AND COPY OF SEARCH REPORT FROM PCT/EP00/05208
    POSTCARD AND EXPRESS MAIL CERTIFICATE

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/018372	PCT/EP00/05208	740-X01-004

21. ☒ The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	14 - 20 =	0	x **$18.00**	$	
Independent claims	1 - 3 =	0	x **$84.00**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$280.00**	$	

TOTAL OF ABOVE CALCULATIONS =	$ 890.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +	$	
SUBTOTAL =	$ 890.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	$	
TOTAL NATIONAL FEE =	$ 890.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +	$ 40.00	
TOTAL FEES ENCLOSED =	$ 930.00	
	Amount to be refunded:	$
	charged:	$

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 500601 in the amount of $ 930.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 500601 . A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

MARTIN FLEIT
Fleit, Kain, Gibbons, Gutman & Bongini P.L.
520 Brickell Key Drive #A201
Miami, FL 33131

Tel (305) 536-9020; Fax (305) 536-9022
Email mfleit@fleitkain.com

SIGNATURE
Martin Fleit By: Paul D. Bianco Reg# 43,500

NAME

16,900
REGISTRATION NUMBER

PATENT

Attorney Docket No.: 740-X01-004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Dirk-Henning MENZ *et al.*

Serial No.: New Patent Application; National Stage of PCT No. PCT/EP00/05208

Group Art Unit:

Filed: December 12 2001

Examiner:

For/Title: PLASTICALLY DEFORMABLE IMPLANT

PRELIMINARY AMENDMENT

BOX PCT
Assistant Commissioner for Patents
Washington, DC 20231

Dear Sir:

Please amend the above-identified application as follows prior to an examination on the merits and calculation of any fees:

In the Specification

Please substitute the attached substitute specification for the specification originally filed. A marked-up copy of the specification showing changes is also attached. The substitute specification does not include any new matter.

In the Claims

Please cancel claims 1-11 and add the following new claims:

12. (New) A plastically deformable implant for insertion into bodily orifices of a human or animal body, the implant formed by a gel which is not sealed and is directly introduced into a natural or artificially created bodily opening, with the gel having a polyaphron structure and comprising a fluorocarbon, water, and a minimum of one fluorinated surface-active agent of the general formula R_FF_{pol}, wherein:

R_F stands for linear or branched perfluoroalkyl groups with more than 5 carbon atoms;

R_{pol} stands for a polar hydrocarbon residue with a minimum of one functional group which is selected from the group consisting of CO-NH(R), $CO\text{-}N(R)_2$, COO-, COOR, SO_3-, $SO_2N(R)_2$, and CH_2-O-R, PO_2H, PO_3H (R = alkyl); and

the surface-active agent has a molecular weight of >400 g/mol, a surface tension in aqueous solution of <30 mN/m, an interfacial tension in aqueous solution with respect to the non-polar component of <25 mN/m, and a concentration of <0.3%.

13. (New) The implant of claim 12 wherein the fluorocarbon is a perfluorocarbon or a partially fluorinated alkane.

14. (New) The implant of claim 12 wherein the fluorocarbon is an oligomer.

15. (New) The implant of claim 12 wherein the surface-active agent is soluble in the fluorocarbon and contains linear or branched perfluoroalkyl groups with more than 5 carbon atoms, and wherein the fluorocarbon and the surface-active agent contain less than 30% of a fluorinated surface-active agent.

16. (New) The implant of claim 12 wherein the gel has a viscosity to density ratio greater than 0.1 Pa cm^3/g and lower than 3 Pa cm^3/g.

17. (New) The implant of claim 16 wherein the ratio is lower than 1 Pa cm^3/g.

18. (New) The implant of claim 12 wherein after liquefaction the gel structure is reversible and can be completely restored.

19. (New) The implant of claim 12 wherein the implant is an ophthalmologic implant.

20. (New) The implant of claim 19 wherein the implant is a vitreous body or lens replacement.

21. (New) The implant of claim 20 wherein the implant is permeable by water-soluble and ionic compounds and has a refractive index in a range from 1.334 to 1.338 and a specific weight greater than 1.05 g/cm^3.

22. (New) The implant of claim 12 wherein the implant is a dental implant.

23. (New) The implant of claim 22 wherein the implant is configured and dimensioned for filling extraction cavities in the jaw bone.

24. (New) The implant of claim 12 wherein the implant is a tissue expander.

25. (New) A method of performing oxygen therapy of tissue comprising the step of inserting the implant of claim 12 into a bodily orifice located proximal the tissue.

Remarks

The specification has been amended to add section headings. The claims have been canceled and new claims have been added to conform the claims to United States patent practice and remove multiple dependencies. No new matter has been added.

Respectfully submitted,

Martin Fleit, Reg. #16,900

By: Paul D. Bianco, Reg. #43,500

Martin Fleit
FLEIT KAIN GIBBONS GUTMAN & BONGINI
520 Brickell Key Drive #A201
Miami, Florida 33131
Tel: 305-536-9020; Fax: 305-536-9022
e-mail: MFleit@FleitKain.com

PATENT

Attorney Docket No.: 740-X01-004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Dirk-Henning MENZ *et al.*

Serial No.: New Patent Application; National Stage of PCT No. PCT/EP00/05208

Group Art Unit:

Filed: December 12 2001

Examiner:

For/Title: PLASTICALLY DEFORMABLE IMPLANT

SUBSTITUTE SPECIFICATION

PLASTICALLY DEFORMABLE IMPLANT

Field of the Invention

[0001] The invention relates to a plastically deformable implant.

Background of the Invention

[0002] Such plastically deformable implants are used, for example, in ophthalmology, in particular as vitreous body or lens replacement, and in dentistry, for example, for filling cavities left after tooth extraction in the jaw bone.

[0003] In addition, in plastic surgery, it is known to use deformable implants which, however, invariably comprise a cushion-like envelope and an implant material as a filler, thus providing a barrier with respect to the surrounding tissue and thereby ensuring biocompatibility.

[0004] For ophthalmological applications, fluorine-containing compounds in the form of readily moving liquids and preparations are known. In this field of application, the properties typical for fluorine-containing compounds, such as high density and low surface tension, are utilized. The partially fluorinated and perfluorinated compounds so far used, however, are single-phase liquids. As a result, varying material properties can be utilized only to the extent defined by the structure and the inherent properties of the chemical compounds used. Thus, with the conventionally known fluorine-containing ophthalmological preparations it is not possible to meet the frequently highly different and in part opposite requirements of the preparation with one single material component.

[0005] Thus, for example, during and after vitreoretinal interventions, a preparation is needed which has excellent tamponade properties and, at the same time, offers the possibility of an exchange of water-soluble substances, which cannot be simultaneously achieved with the well-known ophthalmological preparations since these do not mix with water. In addition, an attempt was made to avoid injury to the retina -- which is observed during the ophthalmological application of perfluorocarbons and which is to be attributed to mechanical effects -- by using substances with a lower density, such as those described in European Patent No. 563 446 B1 and German Patent Nos. DE 197 19 280 and DE 195 36 504 A1. Unfortunately, this entailed a simultaneous increase in the lipophilic properties of these compounds, which led to penetration. As a result, histological changes as well as side effects similar to those known from perfluorocarbons were observed.

[0006] In addition, in prior art, it has been known to use fluorine-containing gels of the class of fluorocarbon-water emulsions. Emulsions in the form of gels of this type and their possible applications in medicine and technology have been described, for example, in U.S. Patent No.

5,573,757, in European Patent No. EP 0 340 079, and in International Patent No. WO 97/03644. These gels form polyaphron structures with a continuous minority phase and a discontinuous majority phase. During this process, the minority phase completely encapsulates the majority phase and thus determines the most important properties of the overall preparation. As known from prior art, a very specific working sequence must be followed in order to produce preparations with this type of structure. Furthermore, it is also known from prior art that in gels of this type, a destruction or liquefaction, for example, by means of heat or mechanical pressure, is irreversible, i.e., once a gel has been destroyed, its original gel structure cannot be restored. This has been described in articles published by M. P. Kraff and J. G. Riess in Angew. Chem. 106 (1994), p. 1146, and by H. Hoffmann and G. Ebert in Angew. Chem. 100 (1988), p. 933.

[0007] In addition, the fluorine-containing gels known from prior art have an affinity both to water and to body tissues. When such gels are used over long periods of time in aqueous media or in body tissue, this affinity to water and tissue leads to a liquefaction and destruction of the gels. This, together with the fact that the gel, once destroyed, cannot have its structure restored since the destruction is irreversible prevents the long-term use of this gel as an implant in body tissue.

Summary of the Invention

[0008] Thus, the problem to be solved by the present invention is to make available a plastically deformable implant which can be inserted into natural or artificially created bodily orifices of the human or animal body and which at the same time is also suitable for long-term use.

[0009] This problem is solved by the characterizing clauses of Claim 1. Useful embodiments and applications of the implant according to the present invention can be taken from the dependent claims.

Detailed Description of the Embodiments

[0010] Because of their versatile and variable properties, the fluorine-containing gels described above are suitable for use as a starting material in the construction of a generic implant. For such an implant to be of long-term use, however, it must be ensured that the implant does not irreversibly liquefy when exposed to aqueous media. In addition, the implant must have a long-term stability to mechanical and thermal stresses. The stability of the implant material on exposure to heat must be ensured, in particular, because the material must be sterilized (121°C) prior to inserting it into the bodily orifices. One finding on which the present invention is based relates to the fact that the gel structure of certain fluorine-containing gels is reversible and can be

completely recovered even after it has been considerably damaged. Compared to the prior printed publications on fluorine-containing gels, this finding comes as a surprise.

[0011] According to the present invention, the term fluorine-containing gel is defined as a gel-like preparation which comprises a minimum of one fluorocarbon. In especially useful embodiments of the present invention, the fluorine-containing gel comprises essentially three components, i.e., a fluorocarbon, a fluorine-containing surface-active agent, and water. It is possible for different additives to be added to the fluorocarbon-containing and aqueous components. Certain compositions of surface-active agents, fluorocarbons, and water form gels which are able to completely recover their gel structure after they have been liquefied, for example, by exposure to mechanical pressure or heat. This property of the gels according to the present invention makes it possible for them to be used as a generic implant over a long period of time. If the implant material of such an implant that has been inserted into a bodily orifice were to liquefy, for example, as a result of short-term pressure, the gel structure, due to the reversibility described, would be able to recover when in a state of rest. Thus, the implant according to the present invention has a self-regulating restorative mechanism. This self-regulating restorative mechanism of a polyaphron gel is attributable to the stability of the aphrons that form the gel. After liquefaction, a gel can restore its structure only if its "building blocks," the aphrons, were not completely destroyed. If a sufficient number of intact aphrons remain after liquefaction, a recovery is possible, and what comes as a surprise is the fact that the aphron structure is transferred to the homogenized regions of the surrounding liquid and that the gel structure is restored in the entire liquid. The stability of the aphrons depends on the intensity of the interaction between water, surface-active agent, and perfluorocarbon, which in turn is determined by the surface properties and the ability of the individual phases to spread on each other's surface. In addition, an important aspect is the intensity of the interactions of the molecules within the films that envelop the aphrons (water/surface-active agent; perfluorocarbon/surface-active agent). Thus, the self-regulating restorative mechanism is activated only if the surface properties of the surface-active agent/water and/or surface-active agent/perfluorocarbon film, on the one hand, and of the internal aphron phase, on the other hand, are properly coordinated, i.e., if the strength of the surface-active agent stabilizes the aphron structure. This can be implemented through the use of fluorine-containing surface-active agents of the general formula

$$R_F\text{-}R_{pol},$$

where R_F stands for the linear or branched perfluoroalkyl groups with more than 5 carbon atoms and R_{pol} stands for a polar hydrocarbon residue which comprises a minimum of one functional group which is selected from CO-NH(R), CO-N$(R)_2$, COO-, COOR, SO_3; $SO_2N(R)_2$, CH_2-O-R,

PO_2H, PO_3H. The molecular weight is preferably >400 g/mol, the surface tension in aqueous solution is <30 mN/m and preferably <20 mN/m. The interfacial tension in aqueous solution with respect to the nonpolar component is <25 mN/m, preferably <10 mN/m, and the concentration is <3%, preferably <0.1%. With nonfluorinated surface-active agents, this can be achieved by means of a strong cohesive effect with an HLB value greater than 25 (HLB = hydrophilic lipophilic balance according to Griffin in J. Soc. Cosmet. Chem. 1 (1949), p. 311).

[0012] Thus, the implant according to the present invention is able to resist both thermal stress, for example, during sterilization, and mechanical stress, for example, pressure exerted on the bodily orifice. Furthermore, the ability of the implant according to the present invention to reverse the damage to its structure prevents the destruction of the implant material that is caused by diffusion processes in the bodily orifices. In the implants according to the present invention, the light transmittance of the fluorine-containing gels which in other gels is generally considerably impaired as a result of these diffusion processes remains in a dynamic equilibrium.

[0013] The biocompatibility of the implants according to the present invention is ensured since ultrapurified starting materials and very small quantities of surface-active agents (preferably <0.1%) are used. Moreover, the surface-active agents used are histocompatible, intimately bonded to the gel, and homogeneously distributed throughout the entire volume.

[0014] The implant according to the present invention is used, for example, in ophthalmology as a vitreous body replacement. For this purpose, in particular fluorine-containing gels with a high specific weight and, at the same time, a high affinity to water-soluble substances are suitable. Thus, for the first time, a tamponading material or implant with a specific weight higher than that of water and, at the same time, the capacity to absorb water-soluble ions are made available. After vitrectomy and conventional procedures of retinal surgery, the plastically deformable implant is injected into the space of the vitreous body. As a result of the absorption of water, the plastically deformable implant expands. The increase in volume caused by the absorption of water enhances the tamponade effect mediated by the highly dense fluorocarbons. At the same time, pressure builds inside the implant, and this pressure counteracts a further expansion in volume and absorption of water. The dynamic equilibrium that is established as a result is ensured by the structural reversibility of the implant material and thus makes it possible for the implant to be used for long-term applications.

[0015] An additional advantage of the implant according to the present invention when used as a vitreous body replacement is the reduction of mechanical injuries in the region of the retina. Such injuries are known to arise when pure fluorocarbons are used as vitreous body replacement materials and have been attributed to the high density of the fluorocarbons. Only recently it was discovered that the injury is not caused by the static pressure. Instead, the injuries are attributable

to the fact that the impalement of heavy fluids on the retina -- as it occurs, for example, when the head is moved rapidly -- causes an increase in the mechanical pressure. When using fluorine-containing gels as vitreous body replacement materials, this effect can be prevented through the use of certain gels. These gels are gels with a high viscosity/density ratio of >100 mPa cm^3/g, preferably >1000 mPa cm^3g. Gels according to the present invention of this type make possible a tamponade in the lower eye segment without the development of motion-induced pressure peaks during sudden jerky head movements. This is made possible by the viscosity which -- in comparison to that of pure fluorocarbons -- is increased, and this increased viscosity counteracts the acceleration forces and prevents the damaging impact of heavy fluids on the retina. In this context, it is a particular advantage that compared to the material properties of pure fluorocarbons, those of the fluorine-containing gels are variable within wide limits.

[0016] In contrast to all other ophthalmological preparations on the basis of fluorinated compounds, the implants according to the present invention as ophthalmological preparations for application in the vitreoretinal region can be used not only in procedures that aim at the reattachment of the retina and as a short-term tamponading material. Instead, in addition to the tamponade effect, these implants can also perform other functions of the natural vitreous body. Thus, these implants open up new possibilities, such as treating pathological changes in the vitreoretinal region or suppressing morbid processes which may lead to a permanent injury to the retina, e.g., injury to the Müller cells. For this purpose, the preparations can be designed to ensure that they combine different and even opposite properties in such a way that these can be activated in one single treatment step. The application potential of the gels is enhanced and expanded by the fluorocarbons that are contained in the gels which, as is well known, have special properties, such as anti-inflammatory and anti-gas properties.

[0017] The other known properties of fluorine-containing compounds that are of advantage when such compounds are applied as ophthalmological preparations are maintained or even enhanced in the implants according to the present invention, thus, for example, the possibility of a laser treatment, the tamponade properties, and the solubility of active ingredients. The implants according to the present invention can be removed from the bodily orifices using conventional methods, for example, vitrectomy.

[0018] The fluorine-containing implants according to the present invention can also be used as intraocular lenses. For this particular purpose, it is recommended that highly transparent gels be used which have an especially high viscosity/density ratio; this can be achieved in particular through the use of oligomer R_FF_H compounds as the discontinuous phase, such as has been described in the European Patent No. EP-A 545 174. In addition, the refractive index of the gels

used should be adjusted to a range from 1.334 to 1.338, which can be implemented, for example, by using the following compounds:

Fluorocarbon	Surface-active agent Name/structure/abbreviation/ characteristics	Refractive index	Biocompatibility (Draize test)
Perfluorophenanthrene	Perfluoroalkyl ethanol oxethylate (Fluowet OTN, Clariant) σ_O = 18 mNm, σ_G = 19 mNm	1.3357	n.d.
Perfluorophenanthrene	Fluorinated amine oxide (Fluowet OX, Clariant) σ_O = 22 mNm, σ_G = 12 mNm	1.3361	n.d.
Perfluorophenanthrene	Perfluoroalkyl ethanol oxethylate (Fluowet OTL, Clariant) σ_O = 19 mNm, σ_G = 10 mNm	1.3355	neg.
Perfluorophenanthrene	Perfluorooctanoic acid tetraethyl piperazinium salt (HO224) σ_O = 16 mNm	1.3362	neg.
Perfluorophenanthrene	Perfluorooctanoic acid N-methyl-D-glucamide (T14) σ_O < 20 mNm	1.3360	neg.
Perfluorophenanthrene	Perfluorooctanoic acid diethanolamide (HO31) σ_O < 20 mNm	1.3358	neg.
Perfluorophenanthrene	Tetramethyl ammonium salt of perfluorooctanoic acid (E 749) σ_O < 20 mNm	1.336	neg.
Perfluorophenanthrene	Perfluorooctanoic acid amidotrimethyl ammonium iodide (B98) σ_O < 20 mNm	1.336	neg.
Perfluorophenanthrene	Tetraethyl ammonium salt of perfluorooctanesulfonic acid (B248) σ_O < 20 mNm	1.3359	neg.
Perfluorophenanthrene	Perfluorodecanoic acid N-(2-hydroxyethyl)-D-glucamide (T21) σ_O < 20 mNm	1.3357	neg.
Perfluorophenanthrene	Perfluorooctanoic acid N-(2-hydroxyethyl)-D-	1.336	neg.

	glucamide (T16) σ_O < 20 mNm		
$C_6P_{13}C_8H_{17}$	Tetramethyl ammonium salt of perfluorooctanoic acid (E749) σ_O < 20 mNm	1.3463	n.d.
$(C_6F_{13}C_2H_4)_3$	Tetramethyl ammomium salt of perfluorooctanoic acid (E 749) σ_O < 20 mNm	1.3357	n.d.

neg. = negative

n.d. = not determined

σ_O = surface tension

σ_G = interfacial tension with respect to the nonpolar component

[0019] The implants according to the present invention can be used instead of the artificial intraocular lenses made of silicone, PMMA, or acrylic that are normally used for cataract operations. After opening the capsular sac and removing the cloudy natural lens using conventionally known methods, the implant material is injected, ensuring that the entire capsular sac is completely filled with it. The implant takes over the complete function of the natural lens, i.e., in spite of the cataract operation, the accommodative capacity of the lens is maintained. Due to the forces that are continuously acting on the implant, the mechanical long-term stability is of very special importance in this particular application.

[0020] The implants according to the present invention can also be used to temporarily seal off bodily orifices and to temporarily separate tissue parts, for example, in applications in which the implants are used as expanders, or to stimulate the growth of bone. In dentistry, the implant according to the present invention can be used in particular to temporarily fill extraction cavities in the jaw bone and to expand tissue. In addition, it can be used in orthopedic medicine as a biocompatible lubricating film for joints and joint prostheses. After inserting the implant material into the extraction cavities, these cavities are encapsulated by sewing together the surrounding tissue. This prevents leakage of the gel-like implant.

[0021] The practical examples described below will explain the choice of the implant materials and their preparation in greater detail. In the explanation, reference is made to the accompanying drawings. As can be seen, these drawings include:

[0022] Figure 1: Measurement of pressure peaks during the acceleration of perfluorophenanthrene in a sealed glass tube, end-scale deflection corresponds to 70 mbar (52.5 mm Hg).

[0023] Figure 2: Measurement of pressure peaks during the acceleration of an implant material according to the present invention in a sealed glass tube, end-scale deflection corresponds to 70 mbar (52.5 mm Hg).

Example 1

[0024] Using ultrasound, a mixture of 99% fluorocarbon, 0.9% isotonic physiological saline solution, and 0.1% OTL is prepared from perfluorophenanthrene which has been ultrapurified according to a well-known method (European Patent No. EP 0 626 936 B1), isotonic physiological saline solution and Fluowet OTL (firm of Clariant); a polyaphron gel in a volume concentration of less than 30% which has been prepared according to conventional methods is slowly added to this solution until the entire mixture solidifies to form a gel. The preparation turns completely transparent after the gas is carefully removed from it or it is centrifuged.

[0025] By subjecting this implant material to alternating mechanical stresses, such as heating to approximately 130° and/or adding water, it is possible to completely liquefy the material. By adding light mechanical energy or cooling or removing water through an absorbent material (dry glass filter, etc.), the gel is returned to its original state. This procedure can be repeated several times, without changing the composition of the plastically deformable implant material.

Example 2

[0026] A plastically deformable implant material which has been prepared according to the instructions described in Example 1 is covered with twice the quantity of water. As a result, the gel-like phase expands. When the volume is limited, e.g., by a semipermeable bottom, an increased pressure begins to build up inside the material until the water on which pressure is exerted from one side exits and flows off on the other side, without destroying the gel structure.

Example 3

[0027] An implant material which has been prepared according to the instructions described in Example 1 and which contains T14 instead of OTL (firm of Clariant), is covered with three times the quantity of water. Instead of the original phase boundary, a thin third phase forms. By especially adjusting the diffusion rates from the boundary layer of the implant and the depth of the volume of gel, it is possible to obtain a perfluorophenanthrene barrier layer which prevents a further dilution of the gel or the breakdown of the gel. This ensures that a stability over a very long time is achieved.

Example 4

[0028] A gel which has been prepared according to the instructions described in Example 1 is placed into a glass tube which can be sealed on both ends. A sensitive pressure sensor is coupled to one end of the glass tube. Subsequently, the glass tube is shaken and positioned so as to ensure that alternately one of the opening points downward. The same test is repeated, except that water and perfluorophenanthrene instead of the plastically deformable implant are used (Figure 1). As a result of the viscosity/density ratio of >3000 mPa cm^3/g, a tamponade effect appropriate to the perfluorocarbons can be achieved by the implant material, without entailing the pressure peaks observed as a result of centrifugal or shaking motions (given an incomplete filling up to 50 mm of mercury), such as are observed with pure perfluorocarbons. In ophthalmological applications, the pressure peaks must not exceed the tolerable intraocular pressure (20, for a short time, 30 mm of mercury). Thus, the plastically deformable implant has a characteristics profile that is highly suitable for use in ophthalmological applications, which profile is a prerequisite for the long-term use as a vitreous body replacement material and, at the same time, it is able to prevent mechanical injury to the retina (Figure 2).

Example 5

[0029] According to the method described in Example 1, it is possible to use, e.g., sodium dodecyl sulfate (SDS) HBL 40 or Pluronic F68 (F68) HLB 29, as surface-active agents in the production of the implants according to the present invention. In both cases the fluorocarbon used is perfluorophenanthrene. The substances can be sterilized at 121°C.

Claims

1. A plastically deformable implant for insertion into bodily orifices of the human or animal body, which implant is formed by a gel containing fluorocarbon, which gel is not sealed and which is directly introduced into the natural or artificially created bodily opening, with the gel having a polyaphron structure and containing, in addition to the fluorocarbon, water and a minimum of one surface-active agent which is a fluorinated surface-active agent of the general formula R_FF_{pol}, where R_F stands for linear or branched perfluoroalkyl groups with more than 5 carbon atoms and R_{pol} stands for a polar hydrocarbon residue with a minimum of one functional group which is selected from CO-NH(R), CO-N$(R)_2$, COO-, COOR, SO_3-; $SO_2N(R)_2$, CH_2-O-R, PO_2H, PO_3H (r = alkyl) with a molecular weight of >400 g/mol, a surface tension of the aqueous solution of <30 mN/m, an interfacial tension in aqueous solution with respect to the nonpolar component of <25 mN/m, and a concentration of <0.3%.

2. The implant as claimed in Claim 1, characterized by the fact that the fluorocarbon is a perfluorocarbon and/or a partially fluorinated alkane.

3. The implant as claimed in one of the preceding claims, characterized by the fact that the fluorocarbon is an oligomer.

4. The implant as claimed in any one of the preceding claims, characterized by the fact that the surface-active agent is soluble in the fluorocarbon, that it contains linear or branched perfluoroalkyl groups with more than 5 carbon atoms, and that the fluorocarbon/surface-active agent component contains less than 30% of a fluorinated surface-active agent.

5. The implant as claimed in any one of the preceding claims, characterized by the fact that the ratio between the viscosity and the density of the gel is greater than 0.1 Pa cm^3/g and lower than 3 Pa cm^3/g, preferably lower than 1 Pa cm^3/g.

6. The implant as claimed in any one of the preceding claims, characterized by the fact that after liquefaction, the structure of the gel is reversible and can be completely restored.

7. The use of an implant as claimed in any one of the preceding claims in ophthalmology, in particular as a vitreous body or lens replacement.

8. The use as claimed in Claim 7, characterized by the fact that the refractive index is in a range from 1.334 to 1.338, that the specific weight is greater than 1.05 g/cm^3, and that the implant is permeable by water-soluble and ionic compounds.

9. The use of an implant as claimed in any one of Claims 1 through 6 in dentistry, in particular for filling extraction cavities in the jaw bone.

10. The use of an implant as claimed in any one of Claims 1 through 6 in the oxygen therapy of the tissue surrounding the bodily orifice.

11. The use of an implant as claimed in any one of Claims 1 through 6 as a tissue expander.

PATENT

Attorney Docket No.: 740-X01-004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Dirk-Henning MENZ *et al.*

Serial No.: New Patent Application; National Stage of PCT No. PCT/EP00/05208

Group Art Unit:

Filed: December 12 2001

Examiner:

For/Title: PLASTICALLY DEFORMABLE IMPLANT

MARKED-UP SPECIFICATION

PLASTICALLY DEFORMABLE IMPLANT

Field of the Invention

The invention relates to a plastically deformable implant [according to the precharacterizing clause of Claim 1].

Background of the Invention

Such plastically deformable implants are used, for example, in ophthalmology, in particular as vitreous body or lens replacement, and in dentistry, for example, for filling cavities left after tooth extraction in the jaw bone.

In addition, in plastic surgery, it is known to use deformable implants which, however, invariably comprise a cushion-like envelope and an implant material as a filler, thus providing a barrier with respect to the surrounding tissue and thereby ensuring biocompatibility.

For ophthalmological applications, fluorine-containing compounds in the form of readily moving liquids and preparations are known. In this field of application, the properties typical for fluorine-containing compounds, such as high density and low surface tension, are utilized. The partially fluorinated and perfluorinated compounds so far used, however, are single-phase liquids. As a result, varying material properties can be utilized only to the extent defined by the structure and the inherent properties of the chemical compounds used. Thus, with the conventionally known fluorine-containing ophthalmological preparations it is not possible to meet the frequently highly different and in part opposite requirements of the preparation with one single material component.

Thus, for example, during and after vitreoretinal interventions, a preparation is needed which has excellent tamponade properties and, at the same time, offers the possibility of an exchange of water-soluble substances, which cannot be simultaneously achieved with the well-known ophthalmological preparations since these do not mix with water. In addition, an attempt was made to avoid injury to the retina -- which is observed during the ophthalmological application of perfluorocarbons and which is to be attributed to mechanical effects -- by using substances with a lower density, such as those described in [the] European Patent No. 563 446 B1 and [the] German Patent Nos. DE 197 19 280 and DE 195 36 504 A1. Unfortunately, this entailed a simultaneous increase in the lipophilic properties of these compounds, which led to penetration. As a result, histological changes as well as side effects similar to those known from perfluorocarbons were observed.

In addition, in prior art, it has been known to use fluorine-containing gels of the class of fluorocarbon-water emulsions. Emulsions in the form of gels of this type and their possible

applications in medicine and technology have been described, for example, in [the] U.S. Patent No. [US] 5,573,757, in [the] European Patent No. EP 0 340 079, and in [the] International Patent No. WO 97/03644. These gels form polyaphron structures with a continuous minority phase and a discontinuous majority phase. During this process, the minority phase completely encapsulates the majority phase and thus determines the most important properties of the overall preparation. As known from prior art, a very specific working sequence must be followed in order to produce preparations with this type of structure. Furthermore, it is also known from prior art that in gels of this type, a destruction or liquefaction, for example, by means of heat or mechanical pressure, is irreversible, i.e., once a gel has been destroyed, its original gel structure cannot be restored. This has been described in articles published by M. P. Kraff and J. G. Riess in Angew. Chem. 106 (1994), p. 1146, and by H. Hoffmann and G. Ebert in Angew. Chem. 100 (1988), p. 933.

In addition, the fluorine-containing gels known from prior art have an affinity both to water and to body tissues. When such gels are used over long periods of time in aqueous media or in body tissue, this affinity to water and tissue leads to a liquefaction and destruction of the gels. This, together with the fact that the gel, once destroyed, cannot have its structure restored since the destruction is irreversible prevents the long-term use of this gel as an implant in body tissue.

Summary of the Invention

Thus, the problem to be solved by the present invention is to make available a plastically deformable implant which can be inserted into natural or artificially created bodily orifices of the human or animal body and which at the same time is also suitable for long-term use.

This problem is solved by the characterizing clauses of Claim 1. Useful embodiments and applications of the implant according to the present invention can be taken from the dependent claims.

Detailed Description of the Embodiments

Because of their versatile and variable properties, the fluorine-containing gels described above are suitable for use as a starting material in the construction of a generic implant. For such an implant to be of long-term use, however, it must be ensured that the implant does not irreversibly liquefy when exposed to aqueous media. In addition, the implant must have a long-term stability to mechanical and thermal stresses. The stability of the implant material on exposure to heat must be ensured, in particular, because the material must be sterilized (121°C) prior to inserting it into the bodily orifices. One finding on which the present invention is based relates to the fact that the gel structure of certain fluorine-containing gels is reversible and can be

completely recovered even after it has been considerably damaged. Compared to the prior printed publications on fluorine-containing gels, this finding comes as a surprise.

According to the present invention, the term fluorine-containing gel is defined as a gel-like preparation which comprises a minimum of one fluorocarbon. In especially useful embodiments of the present invention, the fluorine-containing gel comprises essentially three components, i.e., a fluorocarbon, a fluorine-containing surface-active agent, and water. It is possible for different additives to be added to the fluorocarbon-containing and aqueous components. Certain compositions of surface-active agents, fluorocarbons, and water form gels which are able to completely recover their gel structure after they have been liquefied, for example, by exposure to mechanical pressure or heat. This property of the gels according to the present invention makes it possible for them to be used as a generic implant over a long period of time. If the implant material of such an implant that has been inserted into a bodily orifice were to liquefy, for example, as a result of short-term pressure, the gel structure, due to the reversibility described, would be able to recover when in a state of rest. Thus, the implant according to the present invention has a self-regulating restorative mechanism. This self-regulating restorative mechanism of a polyaphron gel is attributable to the stability of the aphrons that form the gel. After liquefaction, a gel can restore its structure only if its "building blocks," the aphrons, were not completely destroyed. If a sufficient number of intact aphrons remain after liquefaction, a recovery is possible, and what comes as a surprise is the fact that the aphron structure is transferred to the homogenized regions of the surrounding liquid and that the gel structure is restored in the entire liquid. The stability of the aphrons depends on the intensity of the interaction between water, surface-active agent, and perfluorocarbon, which in turn is determined by the surface properties and the ability of the individual phases to spread on each other's surface. In addition, an important aspect is the intensity of the interactions of the molecules within the films that envelop the aphrons (water/surface-active agent; perfluorocarbon/surface-active agent). Thus, the self-regulating restorative mechanism is activated only if the surface properties of the surface-active agent/water and/or surface-active agent/perfluorocarbon film, on the one hand, and of the internal aphron phase, on the other hand, are properly coordinated, i.e., if the strength of the surface-active agent stabilizes the aphron structure. This can be implemented through the use of fluorine-containing surface-active agents of the general formula

$$R_F\text{-}R_{pol},$$

where R_F stands for the linear or branched perfluoroalkyl groups with more than 5 carbon atoms and R_{pol} stands for a polar hydrocarbon residue which comprises a minimum of one functional group which is selected from CO-NH(R), $CO\text{-}N(R)_2$, COO-, COOR, SO_3; $SO_2N(R)_2$, $CH_2\text{-}O\text{-}R$,

PO_2H, PO_3H. The molecular weight is preferably >400 g/mol, the surface tension in aqueous solution is <30 mN/m and preferably <20 mN/m. The interfacial tension in aqueous solution with respect to the nonpolar component is <25 mN/m, preferably <10 mN/m, and the concentration is <3%, preferably <0.1%. With nonfluorinated surface-active agents, this can be achieved by means of a strong cohesive effect with an HLB value greater than 25 (HLB = hydrophilic lipophilic balance according to Griffin in J. Soc. Cosmet. Chem. 1 (1949), p. 311).

Thus, the implant according to the present invention is able to resist both thermal stress, for example, during sterilization, and mechanical stress, for example, pressure exerted on the bodily orifice. Furthermore, the ability of the implant according to the present invention to reverse the damage to its structure prevents the destruction of the implant material that is caused by diffusion processes in the bodily orifices. In the implants according to the present invention, the light transmittance of the fluorine-containing gels which in other gels is generally considerably impaired as a result of these diffusion processes remains in a dynamic equilibrium.

The biocompatibility of the implants according to the present invention is ensured since ultrapurified starting materials and very small quantities of surface-active agents (preferably <0.1%) are used. Moreover, the surface-active agents used are histocompatible, intimately bonded to the gel, and homogeneously distributed throughout the entire volume.

The implant according to the present invention is used, for example, in ophthalmology as a vitreous body replacement. For this purpose, in particular fluorine-containing gels with a high specific weight and, at the same time, a high affinity to water-soluble substances are suitable. Thus, for the first time, a tamponading material or implant with a specific weight higher than that of water and, at the same time, the capacity to absorb water-soluble ions are made available. After vitrectomy and conventional procedures of retinal surgery, the plastically deformable implant is injected into the space of the vitreous body. As a result of the absorption of water, the plastically deformable implant expands. The increase in volume caused by the absorption of water enhances the tamponade effect mediated by the highly dense fluorocarbons. At the same time, pressure builds inside the implant, and this pressure counteracts a further expansion in volume and absorption of water. The dynamic equilibrium that is established as a result is ensured by the structural reversibility of the implant material and thus makes it possible for the implant to be used for long-term applications.

An additional advantage of the implant according to the present invention when used as a vitreous body replacement is the reduction of mechanical injuries in the region of the retina. Such injuries are known to arise when pure fluorocarbons are used as vitreous body replacement materials and have been attributed to the high density of the fluorocarbons. Only recently it was discovered that the injury is not caused by the static pressure. Instead, the injuries are attributable

to the fact that the impalement of heavy fluids on the retina -- as it occurs, for example, when the head is moved rapidly -- causes an increase in the mechanical pressure. When using fluorine-containing gels as vitreous body replacement materials, this effect can be prevented through the use of certain gels. These gels are gels with a high viscosity/density ratio of >100 mPa cm^3/g, preferably >1000 mPa $cm^3 g$. Gels according to the present invention of this type make possible a tamponade in the lower eye segment without the development of motion-induced pressure peaks during sudden jerky head movements. This is made possible by the viscosity which -- in comparison to that of pure fluorocarbons -- is increased, and this increased viscosity counteracts the acceleration forces and prevents the damaging impact of heavy fluids on the retina. In this context, it is a particular advantage that compared to the material properties of pure fluorocarbons, those of the fluorine-containing gels are variable within wide limits.

In contrast to all other ophthalmological preparations on the basis of fluorinated compounds, the implants according to the present invention as ophthalmological preparations for application in the vitreoretinal region can be used not only in procedures that aim at the reattachment of the retina and as a short-term tamponading material. Instead, in addition to the tamponade effect, these implants can also perform other functions of the natural vitreous body. Thus, these implants open up new possibilities, such as treating pathological changes in the vitreoretinal region or suppressing morbid processes which may lead to a permanent injury to the retina, e.g., injury to the Müller cells. For this purpose, the preparations can be designed to ensure that they combine different and even opposite properties in such a way that these can be activated in one single treatment step. The application potential of the gels is enhanced and expanded by the fluorocarbons that are contained in the gels which, as is well known, have special properties, such as anti-inflammatory and anti-gas properties.

The other known properties of fluorine-containing compounds that are of advantage when such compounds are applied as ophthalmological preparations are maintained or even enhanced in the implants according to the present invention, thus, for example, the possibility of a laser treatment, the tamponade properties, and the solubility of active ingredients. The implants according to the present invention can be removed from the bodily orifices using conventional methods, for example, vitrectomy.

The fluorine-containing implants according to the present invention can also be used as intraocular lenses. For this particular purpose, it is recommended that highly transparent gels be used which have an especially high viscosity/density ratio; this can be achieved in particular through the use of oligomer R_FF_H compounds as the discontinuous phase, such as has been described in the European Patent No. EP-A 545 174. In addition, the refractive index of the gels

used should be adjusted to a range from 1.334 to 1.338, which can be implemented, for example, by using the following compounds:

Fluorocarbon	Surface-active agent Name/structure/abbreviation/ characteristics	Refractive index	Biocompatibility (Draize test)
Perfluorophenanthrene	Perfluoroalkyl ethanol oxethylate (Fluowet OTN, Clariant) σ_O = 18 mNm, σ_G = 19 mNm	1.3357	n.d.
Perfluorophenanthrene	Fluorinated amine oxide (Fluowet OX, Clariant) σ_O = 22 mNm, σ_G = 12 mNm	1.3361	n.d.
Perfluorophenanthrene	Perfluoroalkyl ethanol oxethylate (Fluowet OTL, Clariant) σ_O = 19 mNm, σ_G = 10 mNm	1.3355	neg.
Perfluorophenanthrene	Perfluorooctanoic acid tetraethyl piperazinium salt (HO224) σ_O = 16 mNm	1.3362	neg.
Perfluorophenanthrene	Perfluorooctanoic acid N-methyl-D-glucamide (T14) σ_O < 20 mNm	1.3360	neg.
Perfluorophenanthrene	Perfluorooctanoic acid diethanolamide (HO31) σ_O < 20 mNm	1.3358	neg.
Perfluorophenanthrene	Tetramethyl ammonium salt of perfluorooctanoic acid (E 749) σ_O < 20 mNm	1.336	neg.
Perfluorophenanthrene	Perfluorooctanoic acid amidotrimethyl ammonium iodide (B98) σ_O < 20 mNm	1.336	neg.
Perfluorophenanthrene	Tetraethyl ammonium salt of perfluorooctanesulfonic acid (B248) σ_O < 20 mNm	1.3359	neg.
Perfluorophenanthrene	Perfluorodecanoic acid N-(2-hydroxyethyl)-D-glucamide (T21) σ_O < 20 mNm	1.3357	neg.
Perfluorophenanthrene	Perfluorooctanoic acid N-(2-hydroxyethyl)-D-	1.336	neg.

	glucamide (T16) σ_O < 20 mNm		
$C_6P_{13}C_8H_{17}$	Tetramethyl ammonium salt of perfluorooctanoic acid (E749) σ_O < 20 mNm	1.3463	n.d.
$(C_6F_{13}C_2H_4)_3$	Tetramethyl ammomium salt of perfluorooctanoic acid (E 749) σ_O < 20 mNm	1.3357	n.d.

neg. = negative

n.d. = not determined

σ_O = surface tension

σ_G = interfacial tension with respect to the nonpolar component

The implants according to the present invention can be used instead of the artificial intraocular lenses made of silicone, PMMA, or acrylic that are normally used for cataract operations. After opening the capsular sac and removing the cloudy natural lens using conventionally known methods, the implant material is injected, ensuring that the entire capsular sac is completely filled with it. The implant takes over the complete function of the natural lens, i.e., in spite of the cataract operation, the accommodative capacity of the lens is maintained. Due to the forces that are continuously acting on the implant, the mechanical long-term stability is of very special importance in this particular application.

The implants according to the present invention can also be used to temporarily seal off bodily orifices and to temporarily separate tissue parts, for example, in applications in which the implants are used as expanders, or to stimulate the growth of bone. In dentistry, the implant according to the present invention can be used in particular to temporarily fill extraction cavities in the jaw bone and to expand tissue. In addition, it can be used in orthopedic medicine as a biocompatible lubricating film for joints and joint prostheses. After inserting the implant material into the extraction cavities, these cavities are encapsulated by sewing together the surrounding tissue. This prevents leakage of the gel-like implant.

The practical examples described below will explain the choice of the implant materials and their preparation in greater detail. In the explanation, reference is made to the accompanying drawings. As can be seen, these drawings include:

Figure 1: Measurement of pressure peaks during the acceleration of perfluorophenanthrene in a sealed glass tube, end-scale deflection corresponds to 70 mbar (52.5 mm Hg).

Figure 2: Measurement of pressure peaks during the acceleration of an implant material according to the present invention in a sealed glass tube, end-scale deflection corresponds to 70 mbar (52.5 mm Hg).

Example 1

Using ultrasound, a mixture of 99% fluorocarbon, 0.9% isotonic physiological saline solution, and 0.1% OTL is prepared from perfluorophenanthrene which has been ultrapurified according to a well-known method (European Patent No. EP 0 626 936 B1), isotonic physiological saline solution and Fluowet OTL (firm of Clariant); a polyaphron gel in a volume concentration of less than 30% which has been prepared according to conventional methods is slowly added to this solution until the entire mixture solidifies to form a gel. The preparation turns completely transparent after the gas is carefully removed from it or it is centrifuged.

By subjecting this implant material to alternating mechanical stresses, such as heating to approximately 130° and/or adding water, it is possible to completely liquefy the material. By adding light mechanical energy or cooling or removing water through an absorbent material (dry glass filter, etc.), the gel is returned to its original state. This procedure can be repeated several times, without changing the composition of the plastically deformable implant material.

Example 2

A plastically deformable implant material which has been prepared according to the instructions described in Example 1 is covered with twice the quantity of water. As a result, the gel-like phase expands. When the volume is limited, e.g., by a semipermeable bottom, an increased pressure begins to build up inside the material until the water on which pressure is exerted from one side exits and flows off on the other side, without destroying the gel structure.

Example 3

An implant material which has been prepared according to the instructions described in Example 1 and which contains T14 instead of OTL (firm of Clariant), is covered with three times the quantity of water. Instead of the original phase boundary, a thin third phase forms. By especially adjusting the diffusion rates from the boundary layer of the implant and the depth of the volume of gel, it is possible to obtain a perfluorophenanthrene barrier layer which prevents a further dilution of the gel or the breakdown of the gel. This ensures that a stability over a very long time is achieved.

Example 4

A gel which has been prepared according to the instructions described in Example 1 is placed into a glass tube which can be sealed on both ends. A sensitive pressure sensor is coupled to one end of the glass tube. Subsequently, the glass tube is shaken and positioned so as to ensure that alternately one of the opening points downward. The same test is repeated, except that water and perfluorophenanthrene instead of the plastically deformable implant are used (Figure 1). As a result of the viscosity/density ratio of >3000 mPa cm^3/g, a tamponade effect appropriate to the perfluorocarbons can [... [incomplete or grammatically incorrect sentence] ... generate ...] be achieved by the implant material, without entailing the pressure peaks observed as a result of centrifugal or shaking motions (given an incomplete filling up to 50 mm of mercury), such as are observed with pure perfluorocarbons. In ophthalmological applications, the pressure peaks must not exceed the tolerable intraocular pressure (20, for a short time, 30 mm of mercury). Thus, the plastically deformable implant has a characteristics profile that is highly suitable for use in ophthalmological applications, which profile is a prerequisite for the long-term use as a vitreous body replacement material and, at the same time, it is able to prevent mechanical injury to the retina (Figure 2).

Example 5

According to the method described in Example 1, it is possible to use, e.g., sodium dodecyl sulfate (SDS) HBL 40 or Pluoronic F68 (F68) HLB 29, as surface-active agents in the production of the implants according to the present invention. In both cases the fluorocarbon used is perfluorophenanthrene. The substances can be sterilized at 121°C.

Claims

1. A plastically deformable implant for insertion into bodily orifices of the human or animal body, which implant is formed by a gel containing fluorocarbon, which gel is not sealed and which is directly introduced into the natural or artificially created bodily opening, with the gel having a polyaphron structure and containing, in addition to the fluorocarbon, water and a minimum of one surface-active agent which is a fluorinated surface-active agent of the general formula R_FF_{pol}, where R_F stands for linear or branched perfluoroalkyl groups with more than 5 carbon atoms and R_{pol} stands for a polar hydrocarbon residue with a minimum of one functional group which is selected from CO-NH(R), CO-N$(R)_2$, COO-, COOR, SO_3-; $SO_2N(R)_2$, CH_2-O-R, PO_2H, PO_3H (r = alkyl) with a molecular weight of >400 g/mol, a surface tension of the aqueous solution of <30 mN/m, an interfacial tension in aqueous solution with respect to the nonpolar component of <25 mN/m, and a concentration of <0.3%.

2. The implant as claimed in Claim 1, characterized by the fact that the fluorocarbon is a perfluorocarbon and/or a partially fluorinated alkane.

3. The implant as claimed in one of the preceding claims, characterized by the fact that the fluorocarbon is an oligomer.

4. The implant as claimed in any one of the preceding claims, characterized by the fact that the surface-active agent is soluble in the fluorocarbon, that it contains linear or branched perfluoroalkyl groups with more than 5 carbon atoms, and that the fluorocarbon/surface-active agent component contains less than 30% of a fluorinated surface-active agent.

5. The implant as claimed in any one of the preceding claims, characterized by the fact that the ratio between the viscosity and the density of the gel is greater than 0.1 Pa cm^3/g and lower than 3 Pa cm^3/g, preferably lower than 1 Pa cm^3/g.

6. The implant as claimed in any one of the preceding claims, characterized by the fact that after liquefaction, the structure of the gel is reversible and can be completely restored.

7. The use of an implant as claimed in any one of the preceding claims in ophthalmology, in particular as a vitreous body or lens replacement.

8. The use as claimed in Claim 7, characterized by the fact that the refractive index is in a range from 1.334 to 1.338, that the specific weight is greater than 1.05 g/cm^3, and that the implant is permeable by water-soluble and ionic compounds.

9. The use of an implant as claimed in any one of Claims 1 through 6 in dentistry, in particular for filling extraction cavities in the jaw bone.

10. The use of an implant as claimed in any one of Claims 1 through 6 in the oxygen therapy of the tissue surrounding the bodily orifice.

11. The use of an implant as claimed in any one of Claims 1 through 6 as a tissue expander.

ABSTRACT

The invention relates to a plastically deformable implant for inserting into bodily orifices of the human or animal body. Implants of this type are used, for example, in ophthalmology, in particular, as vitreous body or lens replacements and in dentistry, for example, for filling extraction cavities in jaw-bones. Known implants, however, are not suitable for long-term use. The invention aims to provide a deformable plastic implant which also has a long-term application. This is achieved by the fact that the implant consists of a gel which is not sealed, containing fluorocarbon and which is directly introduced into the natural, or artificially created bodily orifice.

1/prts

* * *

The invention relates to a plastically deformable implant according to the precharacterizing clause of Claim 1.

Such plastically deformable implants are used, for example, in ophthalmology, in particular as vitreous body or lens replacement, and in dentistry, for example, for filling cavities left after tooth extraction in the jaw bone.

In addition, in plastic surgery, it is known to use deformable implants which, however, invariably comprise a cushion-like envelope and an implant material as a filler, thus providing a barrier with respect to the surrounding tissue and thereby ensuring biocompatibility.

For ophthalmological applications, fluorine-containing compounds in the form of readily moving liquids and preparations are known. In this field of application, the properties typical for fluorine-containing compounds, such as high density and low surface tension, are utilized. The partially fluorinated and perfluorinated compounds so far used, however, are single-phase liquids. As a result, varying material properties can be utilized only to the extent defined by the structure and the inherent properties of the chemical compounds used. Thus, with the conventionally known fluorine-containing ophthalmological preparations it is not possible to meet the frequently highly different and in part opposite requirements of the preparation with one single material component.

Thus, for example, during and after vitreoretinal interventions, a preparation is needed which has excellent tamponade properties and, at the same time, offers the possibility of an exchange of water-soluble substances, which cannot be simultaneously achieved with the well-known ophthalmological preparations since these do not mix with water. In addition, an attempt was made to avoid injury to the retina -- which is observed during the ophthalmological application of perfluorocarbons and which is to be attributed to mechanical effects -- by using substances with a lower density, such as those described in the European Patent No. 563 446 B1 and the German Patent Nos. DE 197 19 280 and DE 195 36 504 A1. Unfortunately, this entailed a simultaneous increase in the lipophilic properties of these compounds, which led to penetration. As a result, histological changes as well as side effects similar to those known from perfluorocarbons were observed.

In addition, in prior art, it has been known to use fluorine-containing gels of the class of fluorocarbon-water emulsions. Emulsions in the form of gels of this type and their possible applications in medicine and technology have been described, for example, in the U.S. Patent No. US 5,573,757, in the European Patent No. EP 0 340 079, and in the International Patent No. WO 97/03644. These gels form polyaphron structures with a continuous minority phase and a

discontinuous majority phase. During this process, the minority phase completely encapsulates the majority phase and thus determines the most important properties of the overall preparation. As known from prior art, a very specific working sequence must be followed in order to produce preparations with this type of structure. Furthermore, it is also known from prior art that in gels of this type, a destruction or liquefaction, for example, by means of heat or mechanical pressure, is irreversible, i.e., once a gel has been destroyed, its original gel structure cannot be restored. This has been described in articles published by M. P. Kraff and J. G. Riess in Angew. Chem. 106 (1994), p. 1146, and by H. Hoffmann and G. Ebert in Angew. Chem. 100 (1988), p. 933.

In addition, the fluorine-containing gels known from prior art have an affinity both to water and to body tissues. When such gels are used over long periods of time in aqueous media or in body tissue, this affinity to water and tissue leads to a liquefaction and destruction of the gels. This, together with the fact that the gel, once destroyed, cannot have its structure restored since the destruction is irreversible prevents the long-term use of this gel as an implant in body tissue.

Thus, the problem to be solved by the present invention is to make available a plastically deformable implant which can be inserted into natural or artificially created bodily orifices of the human or animal body and which at the same time is also suitable for long-term use.

This problem is solved by the characterizing clauses of Claim 1. Useful embodiments and applications of the implant according to the present invention can be taken from the dependent claims.

Because of their versatile and variable properties, the fluorine-containing gels described above are suitable for use as a starting material in the construction of a generic implant. For such an implant to be of long-term use, however, it must be ensured that the implant does not irreversibly liquefy when exposed to aqueous media. In addition, the implant must have a long-term stability to mechanical and thermal stresses. The stability of the implant material on exposure to heat must be ensured, in particular, because the material must be sterilized (121°C) prior to inserting it into the bodily orifices. One finding on which the present invention is based relates to the fact that the gel structure of certain fluorine-containing gels is reversible and can be completely recovered even after it has been considerably damaged. Compared to the prior printed publications on fluorine-containing gels, this finding comes as a surprise.

According to the present invention, the term fluorine-containing gel is defined as a gel-like preparation which comprises a minimum of one fluorocarbon. In especially useful embodiments of the present invention, the fluorine-containing gel comprises essentially three components, i.e., a fluorocarbon, a fluorine-containing surface-active agent, and water. It is possible for different additives to be added to the fluorocarbon-containing and aqueous

components. Certain compositions of surface-active agents, fluorocarbons, and water form gels which are able to completely recover their gel structure after they have been liquefied, for example, by exposure to mechanical pressure or heat. This property of the gels according to the present invention makes it possible for them to be used as a generic implant over a long period of time. If the implant material of such an implant that has been inserted into a bodily orifice were to liquefy, for example, as a result of short-term pressure, the gel structure, due to the reversibility described, would be able to recover when in a state of rest. Thus, the implant according to the present invention has a self-regulating restorative mechanism. This self-regulating restorative mechanism of a polyaphron gel is attributable to the stability of the aphrons that form the gel. After liquefaction, a gel can restore its structure only if its "building blocks," the aphrons, were not completely destroyed. If a sufficient number of intact aphrons remain after liquefaction, a recovery is possible, and what comes as a surprise is the fact that the aphron structure is transferred to the homogenized regions of the surrounding liquid and that the gel structure is restored in the entire liquid. The stability of the aphrons depends on the intensity of the interaction between water, surface-active agent, and perfluorocarbon, which in turn is determined by the surface properties and the ability of the individual phases to spread on each other's surface. In addition, an important aspect is the intensity of the interactions of the molecules within the films that envelop the aphrons (water/surface-active agent; perfluorocarbon/surface-active agent). Thus, the self-regulating restorative mechanism is activated only if the surface properties of the surface-active agent/water and/or surface-active agent/perfluorocarbon film, on the one hand, and of the internal aphron phase, on the other hand, are properly coordinated, i.e., if the strength of the surface-active agent stabilizes the aphron structure. This can be implemented through the use of fluorine-containing surface-active agents of the general formula

$$R_F\text{-}R_{pol},$$

where R_F stands for the linear or branched perfluoroalkyl groups with more than 5 carbon atoms and R_{pol} stands for a polar hydrocarbon residue which comprises a minimum of one functional group which is selected from CO-NH(R), CO-N$(R)_2$, COO-, COOR, SO_3; $SO_2N(R)_2$, CH_2-O-R, PO_2H, PO_3H. The molecular weight is preferably >400 g/mol, the surface tension in aqueous solution is <30 mN/m and preferably <20 mN/m. The interfacial tension in aqueous solution with respect to the nonpolar component is <25 mN/m, preferably <10 mN/m, and the concentration is <3%, preferably <0.1%. With nonfluorinated surface-active agents, this can be achieved by means of a strong cohesive effect with an HLB value greater than 25 (HLB = hydrophilic lipophilic balance according to Griffin in J. Soc. Cosmet. Chem. 1 (1949), p. 311).

Thus, the implant according to the present invention is able to resist both thermal stress, for example, during sterilization, and mechanical stress, for example, pressure exerted on the bodily orifice. Furthermore, the ability of the implant according to the present invention to reverse the damage to its structure prevents the destruction of the implant material that is caused by diffusion processes in the bodily orifices. In the implants according to the present invention, the light transmittance of the fluorine-containing gels which in other gels is generally considerably impaired as a result of these diffusion processes remains in a dynamic equilibrium.

The biocompatibility of the implants according to the present invention is ensured since ultrapurified starting materials and very small quantities of surface-active agents (preferably <0.1%) are used. Moreover, the surface-active agents used are histocompatible, intimately bonded to the gel, and homogeneously distributed throughout the entire volume.

The implant according to the present invention is used, for example, in ophthalmology as a vitreous body replacement. For this purpose, in particular fluorine-containing gels with a high specific weight and, at the same time, a high affinity to water-soluble substances are suitable. Thus, for the first time, a tamponading material or implant with a specific weight higher than that of water and, at the same time, the capacity to absorb water-soluble ions are made available. After vitrectomy and conventional procedures of retinal surgery, the plastically deformable implant is injected into the space of the vitreous body. As a result of the absorption of water, the plastically deformable implant expands. The increase in volume caused by the absorption of water enhances the tamponade effect mediated by the highly dense fluorocarbons. At the same time, pressure builds inside the implant, and this pressure counteracts a further expansion in volume and absorption of water. The dynamic equilibrium that is established as a result is ensured by the structural reversibility of the implant material and thus makes it possible for the implant to be used for long-term applications.

An additional advantage of the implant according to the present invention when used as a vitreous body replacement is the reduction of mechanical injuries in the region of the retina. Such injuries are known to arise when pure fluorocarbons are used as vitreous body replacement materials and have been attributed to the high density of the fluorocarbons. Only recently it was discovered that the injury is not caused by the static pressure. Instead, the injuries are attributable to the fact that the impalement of heavy fluids on the retina -- as it occurs, for example, when the head is moved rapidly -- causes an increase in the mechanical pressure. When using fluorine-containing gels as vitreous body replacement materials, this effect can be prevented through the use of certain gels. These gels are gels with a high viscosity/density ratio of >100 mPa cm^3/g, preferably >1000 mPa $cm^3 g$. Gels according to the present invention of this type make possible a tamponade in the lower eye segment without the development of

motion-induced pressure peaks during sudden jerky head movements. This is made possible by the viscosity which -- in comparison to that of pure fluorocarbons -- is increased, and this increased viscosity counteracts the acceleration forces and prevents the damaging impact of heavy fluids on the retina. In this context, it is a particular advantage that compared to the material properties of pure fluorocarbons, those of the fluorine-containing gels are variable within wide limits.

In contrast to all other ophthalmological preparations on the basis of fluorinated compounds, the implants according to the present invention as ophthalmological preparations for application in the vitreoretinal region can be used not only in procedures that aim at the reattachment of the retina and as a short-term tamponading material. Instead, in addition to the tamponade effect, these implants can also perform other functions of the natural vitreous body. Thus, these implants open up new possibilities, such as treating pathological changes in the vitreoretinal region or suppressing morbid processes which may lead to a permanent injury to the retina, e.g., injury to the Müller cells. For this purpose, the preparations can be designed to ensure that they combine different and even opposite properties in such a way that these can be activated in one single treatment step. The application potential of the gels is enhanced and expanded by the fluorocarbons that are contained in the gels which, as is well known, have special properties, such as anti-inflammatory and anti-gas properties.

The other known properties of fluorine-containing compounds that are of advantage when such compounds are applied as ophthalmological preparations are maintained or even enhanced in the implants according to the present invention, thus, for example, the possibility of a laser treatment, the tamponade properties, and the solubility of active ingredients. The implants according to the present invention can be removed from the bodily orifices using conventional methods, for example, vitrectomy.

The fluorine-containing implants according to the present invention can also be used as intraocular lenses. For this particular purpose, it is recommended that highly transparent gels be used which have an especially high viscosity/density ratio; this can be achieved in particular through the use of oligomer R_FF_H compounds as the discontinuous phase, such as has been described in the European Patent No. EP-A 545 174. In addition, the refractive index of the gels used should be adjusted to a range from 1.334 to 1.338, which can be implemented, for example, by using the following compounds:

Fluorocarbon	Surface-active agent Name/structure/abbreviation/ characteristics	Refractive index	Biocompatibility (Draize test)
Perfluorophenanthrene	Perfluoroalkyl ethanol	1.3357	n.d.

	oxethylate (Fluowet OTN, Clariant) σ_O = 18 mNm, σ_G = 19 mNm		
Perfluorophenanthrene	Fluorinated amine oxide (Fluowet OX, Clariant) σ_O = 22 mNm, σ_G = 12 mNm	1.3361	n.d.
Perfluorophenanthrene	Perfluoroalkyl ethanol oxethylate (Fluowet OTL, Clariant) σ_O = 19 mNm, σ_G = 10 mNm	1.3355	neg.
Perfluorophenanthrene	Perfluorooctanoic acid tetraethyl piperazinium salt (HO224) σ_O = 16 mNm	1.3362	neg.
Perfluorophenanthrene	Perfluorooctanoic acid N-methyl-D-glucamide (T14) σ_O < 20 mNm	1.3360	neg.
Perfluorophenanthrene	Perfluorooctanoic acid diethanolamide (HO31) σ_O < 20 mNm	1.3358	neg.
Perfluorophenanthrene	Tetramethyl ammonium salt of perfluorooctanoic acid (E 749) σ_O < 20 mNm	1.336	neg.
Perfluorophenanthrene	Perfluorooctanoic acid amidotrimethyl ammonium iodide (B98) σ_O < 20 mNm	1.336	neg.
Perfluorophenanthrene	Tetraethyl ammonium salt of perfluorooctanesulfonic acid (B248) σ_O < 20 mNm	1.3359	neg.
Perfluorophenanthrene	Perfluorodecanoic acid N-(2-hydroxyethyl)-D-glucamide (T21) σ_O < 20 mNm	1.3357	neg.
Perfluorophenanthrene	Perfluorooctanoic acid N-(2-hydroxyethyl)-D-glucamide (T16) σ_O < 20 mNm	1.336	neg.
$C_6P_{13}C_8H_{17}$	Tetramethyl ammonium salt of perfluorooctanoic acid (E749) σ_O < 20 mNm	1.3463	n.d.
$(C_6F_{13}C_2H_4)_3$	Tetramethyl ammomium salt of perfluorooctanoic acid (E 749) σ_O < 20 mNm	1.3357	n.d.

neg. = negative
n.d. = not determined
σ_O = surface tension
σ_G = interfacial tension with respect to the nonpolar component

The implants according to the present invention can be used instead of the artificial intraocular lenses made of silicone, PMMA, or acrylic that are normally used for cataract operations. After opening the capsular sac and removing the cloudy natural lens using conventionally known methods, the implant material is injected, ensuring that the entire capsular sac is completely filled with it. The implant takes over the complete function of the natural lens, i.e., in spite of the cataract operation, the accommodative capacity of the lens is maintained. Due to the forces that are continuously acting on the implant, the mechanical long-term stability is of very special importance in this particular application.

The implants according to the present invention can also be used to temporarily seal off bodily orifices and to temporarily separate tissue parts, for example, in applications in which the implants are used as expanders, or to stimulate the growth of bone. In dentistry, the implant according to the present invention can be used in particular to temporarily fill extraction cavities in the jaw bone and to expand tissue. In addition, it can be used in orthopedic medicine as a biocompatible lubricating film for joints and joint prostheses. After inserting the implant material into the extraction cavities, these cavities are encapsulated by sewing together the surrounding tissue. This prevents leakage of the gel-like implant.

The practical examples described below will explain the choice of the implant materials and their preparation in greater detail. In the explanation, reference is made to the accompanying drawings. As can be seen, these drawings include:

Figure 1: Measurement of pressure peaks during the acceleration of perfluorophenanthrene in a sealed glass tube, end-scale deflection corresponds to 70 mbar (52.5 mm Hg).

Figure 2: Measurement of pressure peaks during the acceleration of an implant material according to the present invention in a sealed glass tube, end-scale deflection corresponds to 70 mbar (52.5 mm Hg).

Example 1

Using ultrasound, a mixture of 99% fluorocarbon, 0.9% isotonic physiological saline solution, and 0.1% OTL is prepared from perfluorophenanthrene which has been ultrapurified

according to a well-known method (European Patent No. EP 0 626 936 B1), isotonic physiological saline solution and Fluowet OTL (firm of Clariant); a polyaphron gel in a volume concentration of less than 30% which has been prepared according to conventional methods is slowly added to this solution until the entire mixture solidifies to form a gel. The preparation turns completely transparent after the gas is carefully removed from it or it is centrifuged.

By subjecting this implant material to alternating mechanical stresses, such as heating to approximately 130° and/or adding water, it is possible to completely liquefy the material. By adding light mechanical energy or cooling or removing water through an absorbent material (dry glass filter, etc.), the gel is returned to its original state. This procedure can be repeated several times, without changing the composition of the plastically deformable implant material.

Example 2

A plastically deformable implant material which has been prepared according to the instructions described in Example 1 is covered with twice the quantity of water. As a result, the gel-like phase expands. When the volume is limited, e.g., by a semipermeable bottom, an increased pressure begins to build up inside the material until the water on which pressure is exerted from one side exits and flows off on the other side, without destroying the gel structure.

Example 3

An implant material which has been prepared according to the instructions described in Example 1 and which contains T14 instead of OTL (firm of Clariant), is covered with three times the quantity of water. Instead of the original phase boundary, a thin third phase forms. By especially adjusting the diffusion rates from the boundary layer of the implant and the depth of the volume of gel, it is possible to obtain a perfluorophenanthrene barrier layer which prevents a further dilution of the gel or the breakdown of the gel. This ensures that a stability over a very long time is achieved.

Example 4

A gel which has been prepared according to the instructions described in Example 1 is placed into a glass tube which can be sealed on both ends. A sensitive pressure sensor is coupled to one end of the glass tube. Subsequently, the glass tube is shaken and positioned so as to ensure that alternately one of the opening points downward. The same test is repeated, except that water and perfluorophenanthrene instead of the plastically deformable implant are used (Figure 1). As a result of the viscosity/density ratio of >3000 mPa cm^3/g, a tamponade effect appropriate to the perfluorocarbons can … [incomplete or grammatically incorrect sentence] ... generate ... by the

implant material, without entailing the pressure peaks observed as a result of centrifugal or shaking motions (given an incomplete filling up to 50 mm of mercury), such as are observed with pure perfluorocarbons. In ophthalmological applications, the pressure peaks must not exceed the tolerable intraocular pressure (20, for a short time, 30 mm of mercury). Thus, the plastically deformable implant has a characteristics profile that is highly suitable for use in ophthalmological applications, which profile is a prerequisite for the long-term use as a vitreous body replacement material and, at the same time, it is able to prevent mechanical injury to the retina (Figure 2).

Example 5

According to the method described in Example 1, it is possible to use, e.g., sodium dodecyl sulfate (SDS) HBL 40 or Pluronic F68 (F68) HLB 29, as surface-active agents in the production of the implants according to the present invention. In both cases the fluorocarbon used is perfluorophenanthrene. The substances can be sterilized at 121°C.

MODIFIED PAGES

Claims

1. A plastically deformable implant for insertion into bodily orifices of the human or animal body, which implant is formed by a gel containing fluorocarbon, which gel is not sealed and which is directly introduced into the natural or artificially created bodily opening, with the gel having a polyaphron structure and containing, in addition to the fluorocarbon, water and a minimum of one surface-active agent which is a fluorinated surface-active agent of the general formula $R_F F_{pol}$, where R_F stands for linear or branched perfluoroalkyl groups with more than 5 carbon atoms and R_{pol} stands for a polar hydrocarbon residue with a minimum of one functional group which is selected from CO-NH(R), CO-$N(R)_2$, COO-, COOR, SO_3-; $SO_2N(R)_2$, CH_2-O-R, PO_2H, PO_3H (r = alkyl) with a molecular weight of >400 g/mol, a surface tension of the aqueous solution of <30 mN/m, an interfacial tension in aqueous solution with respect to the nonpolar component of <25 mN/m, and a concentration of <0.3%.

2. The implant as claimed in Claim 1, characterized by the fact that the fluorocarbon is a perfluorocarbon and/or a partially fluorinated alkane.

3. The implant as claimed in one of the preceding claims, characterized by the fact that the fluorocarbon is an oligomer.

4. The implant as claimed in any one of the preceding claims, characterized by the fact that the surface-active agent is soluble in the fluorocarbon, that it contains linear or branched perfluoroalkyl groups with more than 5 carbon atoms, and that the fluorocarbon/surface-active agent component contains less than 30% of a fluorinated surface-active agent.

5. The implant as claimed in any one of the preceding claims, characterized by the fact that the ratio between the viscosity and the density of the gel is greater than 0.1 Pa cm^3/g and lower than 3 Pa cm^3/g, preferably lower than 1 Pa cm^3/g.

6. The implant as claimed in any one of the preceding claims, characterized by the fact that after liquefaction, the structure of the gel is reversible and can be completely restored.

7. The use of an implant as claimed in any one of the preceding claims in ophthalmology, in particular as a vitreous body or lens replacement.

8. The use as claimed in Claim 7, characterized by the fact that the refractive index is in a range from 1.334 to 1.338, that the specific weight is greater than 1.05 g/cm^3, and that the implant is permeable by water-soluble and ionic compounds.

9. The use of an implant as claimed in any one of Claims 1 through 6 in dentistry, in particular for filling extraction cavities in the jaw bone.

10. The use of an implant as claimed in any one of Claims 1 through 6 in the oxygen therapy of the tissue surrounding the bodily orifice.

11. The use of an implant as claimed in any one of Claims 1 through 6 as a tissue expander.

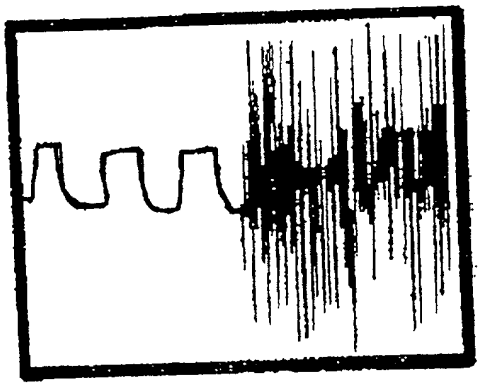

Fig. 1

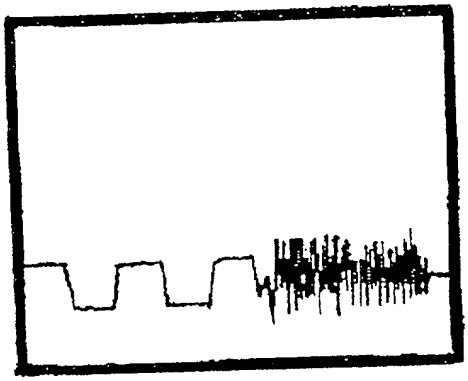

Fig. 2

FKGGB DOCKET No. 740-X01-004

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter that is claimed and for which a patent is sought on the invention entitled

PLASTICALLY DEFORMABLE IMPLANT

the specification of which: (check one)

___ is attached hereto.

__X__ was filed
as International Application No. PCT/EP00/05208
and was amended on May 25, 2001 and October 10, 2000 (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information material to the patentability of this application in accordance with 37 CFR 1.56.

I hereby claim the benefit of foreign priority under 35 USC 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application the priority of which is claimed:

Prior Foreign Application(s):				Priority Claimed	
	Number	Country	Filing Date	Yes	No
✓	199 26 889.4	DE	June 12, 1999	XXX	

I hereby claim the benefit of United States priority under 35 USC 120 of any United States application(s) or 365(c) of any PCT international applications designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is disclosed in a listed one of the prior United States or PCT international application in the manner provided by the first paragraph of 35 USC 112, I acknowledge the duty to disclose information material to the patentability of this

application as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. Parent Application or PCT Parent Number	(Filing Date)	Parent Patent Number
PCT/EP00/05208	June 7, 2000	

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Martin Fleit	Reg. No. 16,900
Paul D. Bianco	Reg. No. 43,500
Robert C. Kain	Reg. No. 30,648
Jon A. Gibbons	Reg. No. 37,333
Stephen C. Bongini	Reg. No. 40,917
Jose Gutman	Reg. No. 35,171

Send correspondence to MARTIN FLEIT, Fleit, Kain, Gibbons, Gutman & Bongini, P.L., 520 Brickell Key Drive, Miami, Florida 33131, and direct all telephone calls to MARTIN FLEIT at (305) 536-9020.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 USC 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

FULL NAME OF INVENTOR: Dirk-Henning MENZ

INVENTOR'S SIGNATURE: Dirk-Henning Menz DATE: 05/12/2001

RESIDENCE: Germany
CITIZENSHIP: Germany
POST OFFICE ADDRESS: Wartheweg 12, D-86420 Diedorf, GERMANY DEX

FULL NAME OF INVENTOR: Joachim DRESP

INVENTOR'S SIGNATURE: J. H. Dresp DATE: 30/11/2001

RESIDENCE: Germany
CITIZENSHIP: Germany
POST OFFICE ADDRESS: Hohenbrunnerstrasse 14, D-81825 Munich, GERMANY DEX